

ORIGINAL ARTICLE

Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with type 2 diabetes mellitus treated with metformin: EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial

Jürgen Harreiter PhD¹  | Ivica Just PhD^{2,3} | Michael Leutner PhD¹ |
Magdalena Bastian BSc¹ | Helmut Brath MD⁴ | Christian Schelkshorn MD⁵ |
Radka Klepochova PhD^{2,3} | Martin Krššák PhD^{2,3} | Alexandra Kautzky-Willer MD¹ 

¹Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Medicine III, Medical University Vienna, Vienna, Austria

²Department of Biomedical Imaging and Image-Guided Therapy, High-Field MR Center, Medical University of Vienna, Vienna, Austria

³Division of Endocrinology and Metabolism, Department of Medicine III, Medical University Vienna, Vienna, Austria

⁴Diabetes Outpatient Clinic, Health Centre Favoriten, Vienna, Austria

⁵Department of Medicine, State Hospital Stockerau, Stockerau, Austria

Correspondence

Jürgen Harreiter, MD, PhD, MSc, Gender Medicine Unit, Division of Endocrinology and Metabolism, Department of Medicine III, Medical University Vienna, Waehringerguertel 18-20, 1090 Vienna, Austria.
Email: juergen.harreiter@meduniwien.ac.at

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Abstract

Aims: To investigate the potential synergistic effects of combined exenatide (EXE) and dapagliflozin (DAPA) versus (PLAC) placebo and DAPA on hepatocellular lipid (HCL) reduction after 24 weeks of treatment.

Materials and methods: Thirty patients with type 2 diabetes were randomized to weekly EXE and daily DAPA (n = 16) or weekly PLAC and daily DAPA (n = 14). Inclusion criteria were glycated haemoglobin (HbA1c) 48 to 97 mmol/mol (6.5-11%), age 18 to 75 years, body mass index (BMI) ≥ 25 kg/m² and metformin ≥ 1000 mg. The primary endpoint, HCL levels, were measured at baseline and after 24 weeks of treatment using magnetic resonance spectroscopy. Between-group effects were analysed using general linear models, adjusted for baseline outcome variables, age, sex and BMI. Within-group differences were assessed using a paired t-test.

Results: After 24 weeks, HCLs were reduced in both treatment groups (absolute change from baseline: EXE + DAPA -4.4%, 95% confidence interval [CI] -8.2, -0.7, $P < 0.05$; PLAC + DAPA -3.9%, 95% CI -6.0, -1.7, $P < 0.01$; relative change: EXE + DAPA -35.6%, PLAC + DAPA -32.3%) with no difference between groups. Similar findings were observed for subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). HbA1c (EXE + DAPA -17.8 mmol/mol, [95% CI -24.8, -10.8], $P < 0.001$; PLAC + DAPA -6.9 mmol/mol, [95% CI -10.5, -3.3], $P = 0.001$) and fasting glucose significantly decreased in both groups, although EXE + DAPA achieved better glycaemic control than PLAC + DAPA (adjusted difference: HbA1c -6.0 mmol/mol [95% CI -9.7, -2.2], $P < 0.01$). Body weight was reduced in both treatment groups (EXE + DAPA -7.3 kg, 95% CI -9.9, -4.8, $P < 0.001$; PLAC + DAPA -4.6 kg, 95% CI -7.4, -1.8, $P < 0.01$) with comparable results between groups.

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Changes in HCLs and weight, hip and waist circumference, VAT and SAT were positively associated.

Conclusion: After 24 weeks, HCLs were significantly but comparably reduced in the EXE + DAPA and PLAC + DAPA groups, despite significantly better glycaemic control in the combined group EXE + DAPA. Changes in HCLs were associated with weight loss and reduction of visceral adiposity, but not with glucose control. Further studies are necessary to evaluate possible additional long-term effects of a combined treatment.

KEYWORDS

CVD, ectopic lipids, GLP-1 receptor agonist, glycaemic control, magnetic resonance imaging, metabolic syndrome, NAFLD, obesity, prevention, SGLT2 inhibitor, type 2 diabetes mellitus, weight loss

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with several comorbidities, such as cardiovascular disease (CVD), obesity, hyperlipidaemia and nonalcoholic fatty liver disease (NAFLD), the most prevalent chronic liver disease worldwide. NAFLD is common among people with T2DM, demonstrating a global prevalence of approximately 55% in this population, with the highest prevalence rates, 70%, reported in Europe.¹ An elevated risk for progression to more severe liver diseases such as nonalcoholic steatohepatitis, fibrosis and cirrhosis, as well as end-stage liver disease, is evident.^{2,3} Recently, a population-based cohort study found a significant increase in the indication for liver transplantation associated with NAFLD from 2.0% to 6.2% over the last three decades.⁴ Facing these complications of NAFLD, interventions that are able to effectively and safely reduce excess hepatocellular lipids (HCLs) need to be identified urgently.

Recent national and international clinical practice guidelines recommend new drug classes, such as sodium-glucose co-transporter 2 (SGLT2) inhibitors or glucagon-like peptide-1 receptor agonists (GLP-1RAs) as the main treatment options in high-risk CVD patients, based on their cardiovascular and renal benefits.⁵⁻⁷ Moreover, disease-modifying effects on NAFLD were reported for several glucose-lowering drugs, including some GLP-1RAs and SGLT2 inhibitors. Indeed, more and more patients in clinical routine are using combined GLP-1RA and SGLT2 inhibitor therapy, showing strong glucose-lowering potential and weight reduction.^{8,9} Whether treatment combinations also have synergistic cardiovascular or renal effects, are more beneficial in patients with heart failure, or are able to reduce HCLs more effectively is not well investigated and thus needs further examination in randomized controlled trials (RCTs).

Nonalcoholic fatty liver disease is associated with increased CVD mortality, and an even higher mortality was reported in patients with both NAFLD and T2DM.^{2,3,10} Thus a dual strategy using glucose-lowering compounds to optimize glycaemic control and to reduce HCL levels seems a promising approach in patients with T2DM. So far, combinations of the abovementioned drug classes to investigate the synergistic effects of these compounds in reducing HCL levels have rarely been examined. One RCT combining exenatide (EXE) and

pioglitazone observed significantly higher reductions in HCLs compared with pioglitazone.¹¹ Recently, a study demonstrated beneficial effects of a combination of the SGLT2 inhibitor dapagliflozin (DAPA) with the GLP-1RA EXE on reducing markers and scores of liver steatosis and fibrosis in patients with T2DM on metformin therapy.¹² However, further studies to validate these findings are required.

In EXENDA, a prospective, single-centre, double-blind, randomized controlled trial, we aimed to investigate the potential synergistic effects of a treatment combination of once-weekly EXE and once-daily DAPA on HCL levels, measured by magnetic resonance spectroscopy (MRS), compared with once-weekly EXE-matched placebo (PLAC) and once-daily DAPA in patients with T2DM and metformin monotherapy after 24 weeks of treatment.

2 | METHODS

2.1 | Study design and participants

EXENDA included both men and women with T2DM ($n = 30$) who met the following criteria: glycated hemoglobin (HbA1c) level ≥ 48 and ≤ 97 mmol/mol (6.5%-11%), age 18 to 75 years, body mass index (BMI) ≥ 25 kg/m², and metformin treatment ≥ 1000 mg daily with a stable dose for at least 8 weeks. Exclusion criteria are shown in the supplementary material section (Appendix S1, supplementary material S1). Patients were recruited from our diabetes outpatient clinic and affiliated hospitals. The study was performed at a single centre, the Medical University of Vienna, and approved by the local research ethics committee (EKNR 1306/2016). EXENDA was registered in approved clinical trial registries (EudraCT 2016-000574-38). The study was conducted in accordance with the ethical and good clinical practice standards of the responsible ethics committee. Informed consent was obtained from all patients and recruitment was conducted between June 2017 and May 2019. In total seven study visits were conducted: a screening visit (week -4 to 0), followed by the randomization visit at baseline (week 0), study visits at 4, 8, 16 and 24 weeks, and a follow-up visit at week 28.

The sample size ($n = 16$ per arm) was determined to detect a 4% change in HCLs between EXE + DAPA and PLAC + DAPA, with 80%

power at a significance level of 5%, based on results of a previously published RCT examining the effects of EXE on excess hepatic fat reduction after 26 weeks of treatment compared with a reference group.¹³

2.2 | Study objectives

The primary objective was to investigate the effects of a combination therapy with EXE + DAPA compared with PLAC + DAPA, given for 24 weeks, on the reduction of HCL levels in patients with T2DM and metformin therapy only. Secondary and exploratory objectives were the investigation of changes in subcutaneous and visceral fat, glycaemic control (change in HbA1c, percentage of patients reaching target HbA1c [≤ 48 mmol/mol]), fasting plasma glucose and fasting plasma insulin, weight loss, waist and hip circumference, liver function variables (alanine transaminase [ALT], aspartate aminotransferase [AST], gamma-glutamyl transpeptidase [GGT]), lipid variables, treatment safety and tolerability.

2.3 | Randomization and blinding

Patients were randomized in a 1:1 ratio and stratified by BMI ($<30/ >30$ kg/m²) to either combined EXE + DAPA or PLAC + DAPA with a Good Clinical Practice-compliant computer randomization program (www.randomizer.at), applying a block randomization in permuted blocks of six. The unique coding key was only known by the programmer, who was not working with the study staff or patients enrolled in this study. The study staff received electronic information of the actual randomization of the patient via email after logging into the electronic randomization tool with their own access codes. They received one unique number assigning the patient to either treatment group in a blinded fashion.

2.4 | Interventions

Dapagliflozin was distributed in the officially approved original boxes available in Austria. Both groups received DAPA via a similar route, and with a similar dosage and frequency, and thus it was not randomized. The investigational drugs were provided by AstraZeneca. EXE and PLAC were identical in appearance and did not differ in colour, smell or handling. Participants were randomized to receive either EXE + DAPA ($n = 16$) or PLAC + DAPA ($n = 14$) for a total duration of 24 weeks. The initial and maintenance doses of EXE and PLAC were 2 mg. EXE/PLAC was administered subcutaneously once weekly by the patients. The study participants received guided application training of EXE/PLAC using material provided by AstraZeneca. The initial and maintenance doses of DAPA were 10 mg. DAPA was administered orally once daily. Treatment compliance was documented with drug accountability and by asking patients directly, as well as by measurement of urinary glucose to document regular

SGLT2 inhibitor intake. Participants were also asked to bring empty blisters and used vials to the study visits to check compliance with medication intake.

2.5 | Assessments

Blood sampling, laboratory methods and calculations of insulin resistance and NAFLD/fibrosis scores are described in detail in the supplementary material section (Appendix S1, supplementary material S2).

2.6 | Assessment of lipid distribution by MRS

All measurements were performed using a 3-Tesla whole-body scanner (Magnetom PrismaFit; Siemens Healthcare, Erlangen, Germany). Participants were placed supine with the head first, and a combination of spine array coil and flex coil was placed over the upper abdomen. MRS measurements were performed at baseline and after 24 weeks. HCLs were measured using a localized short echo time 1H single-voxel spectroscopy sequence, similarly to previous studies, without water signal suppression during single breath hold by placing the volume of interest within the right lateral liver lobe.^{14,15} Signals of lipids from both (CH₂)_n (1.3 ppm) and CH₃ (0.9 ppm) group resonances and water (4.7 ppm) were corrected for T₁ and T₂ relaxation, with relaxation times measured at 3-Tesla. HCL values were calculated from the processed signals as the fat fraction percentage ratio between lipids and the sum of water and lipid integrals. A hepatic triglyceride threshold of $\geq 5.56\%$ was used to assess hepatic steatosis, based on previous work.¹⁶

Visceral and subcutaneous abdominal fat (visceral adipose tissue [VAT] and subcutaneous adipose tissue [SAT]) were measured with an axial T₁-weighted turbo spin echo technique using the whole-body coil of the MRI system. Within one breath hold, 10 slices of 10-mm thickness and 10-mm gap were recorded, covering the area from the sacroiliacum to L1. SAT and VAT were quantified in three slices (L5/L4, L4/L3 and L3/L2) by semiautomatic delineation of the compartments in ImageJ software.¹⁷

2.7 | Statistical analyses

Continuous variables were summarized using means and standard deviations, and categorical variables by counts and percentages. Assumption of Gaussian distribution of parameters was decided using a Kolmogorov-Smirnov test. Nonparametrically distributed parameters were log-transformed. Baseline categorical and continuous variables were analysed using a chi-squared test or Student's *t*-test as appropriate. Associations were tested using Pearson correlation analysis. Differences between treatment groups after 24 weeks were tested using analysis of covariance (ANCOVA), with treatment as a fixed factor and adjustment for the baseline outcome as a covariate. Adjustment for sex, age and BMI was conducted in a further statistical

model. Within-group effects from baseline to end of study were assessed with a paired *t*-test. The efficacy analysis was based on the intention-to-treat population. To test the robustness of the results, per-protocol sensitivity analyses were performed. Last observation carried forward was used to substitute missing results. Treatment efficacy and safety between treatment groups was assessed by logistic regression models. Statistical analysis was performed using SPSS 26.0 (SPSS Inc. Chicago, Illinois) and GraphPad Prism 7 (GraphPad Software, La Jolla, California). A two-sided *P* value <0.05 was considered statistically significant.

3 | RESULTS

Thirty participants were randomized to EXE + DAPA (*n* = 16) or PLAC + DAPA (*n* = 14). One participant in the PLAC + DAPA group was excluded because this individual withdrew from the study after the baseline visit (Figure 1). The baseline characteristics of the two groups were comparable (Table 1). The majority of the participants were of White ethnicity (97%) and 33% were women. All participants were on metformin only before entering the study. The mean diabetes disease duration was 6.6 years.

3.1 | HCLs, visceral and subcutaneous adipose lipids

After 24 weeks of treatment no significant differences were found in HCL levels between the treatment groups (Table 2, Figure 2). However, in both treatment groups, HCL level significantly decreased from baseline (Table 3). Hepatic steatosis resolved (participants with <5.56% HCLs) in five of 30 (16.7%) participants (EXE + DAPA: 3/16, 14.3%, PLAC + DAPA: 2/14, 18.8%; *P* = 0.74). VAT and SAT were reduced significantly in both the EXE + DAPA and the PLAC + DAPA groups, but no differences in VAT and SAT were observed between groups (Tables 2 and 3, Figure 2). Per-protocol analysis showed comparable results (data not shown). Relative changes in HCLs, VAT, SAT and metabolic variables are presented by treatment group in the supplementary material section (Appendix S1, supplementary material S3). Characteristics of participants more responsive and less responsive to treatment (both treatment arms) discriminated by the 50th percentile of HCL reduction are also shown in the supplementary material section (Appendix S1, supplementary material S4). Baseline characteristics were similar in the two groups. High responders had significantly greater weight loss and greater reductions in waist circumference, VAT and SAT, whereas glycaemic variables were comparable.

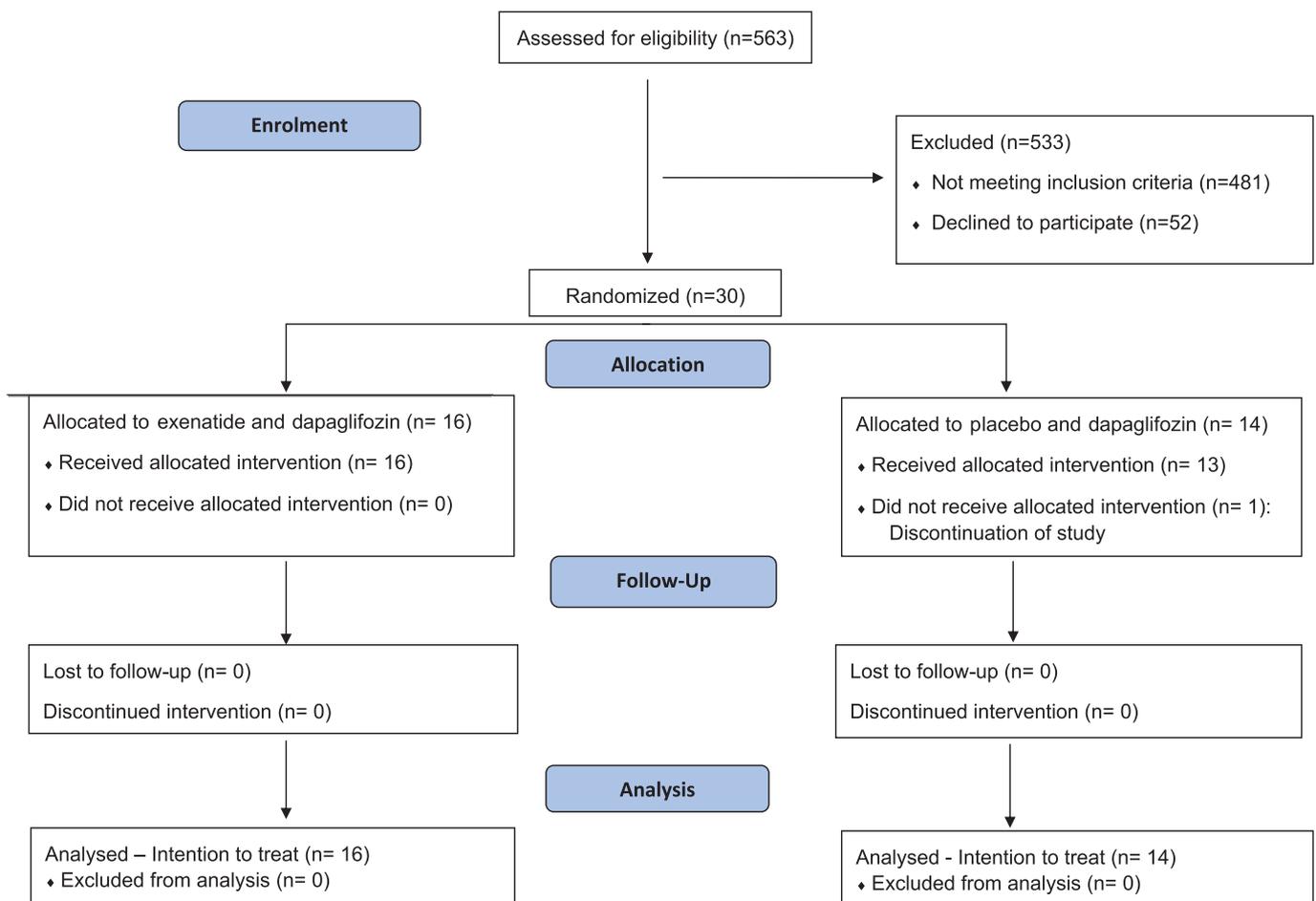


FIGURE 1 Enrolment and group allocation chart

TABLE 1 Baseline characteristics of the study population

	EXE + DAPA			PLAC + EXE			All			P
	n	Mean	SD	N	Mean	SD	n	Mean	SD	
Lipid distribution										
HCLs, %	16	12.85	9.26	14	13.17	8.91	30	13.00	8.94	0.92
VAT, mm ² *	14	8.33	3.12	12	8.49	3.28	26	8.41	3.13	0.90
SAT, mm ² *	14	18.36	5.20	12	16.55	4.95	26	17.52	5.07	0.38
Glycaemic variables										
Fasting glucose, mmol/l*	16	9.4	4.0	14	8.3	1.7	30	8.9	3.1	0.36
Fasting insulin, μU/mL*	16	14.8	11.3	14	14.7	9.3	30	14.7	10.2	0.98
HbA1c, mmol/mol	16	62.2	15.0	14	55.9	6.8	30	59.2	12.2	0.16
HbA1c, %	16	7.8	1.3	14	7.3	0.6	30	7.5	1.0	0.17
HOMA-IR *	16	6.4	5.9	14	5.6	4.0	30	6.0	5.1	0.67
Diabetes duration, years	16	7.3	5.2	14	5.8	4.7	30	6.6	5.0	0.43
Anthropometrics										
Age, years	16	59.4	8.5	14	60.9	7.4	30	60.1	7.9	0.63
Height, cm	16	175.6	0.1	14	174.3	0.1	30	175	0.1	0.72
Weight, kg	16	99.1	20.6	14	93.5	14.2	30	96.5	17.9	0.40
BMI, kg/m ²	16	31.9	4.6	14	30.7	3.5	30	31.3	4.1	0.45
Neck circumference, cm	16	41.9	4.4	14	41.6	3.4	30	41.7	3.9	0.83
Waist circumference, cm	16	113.0	12.3	14	111.3	8.9	30	112.2	10.7	0.67
Hip circumference, cm*	16	113.1	11.0	14	111.0	8.3	30	112.1	9.8	0.56
Blood pressure, mmHg										
Systolic	16	137	15	14	131	18	30	134	16	0.34
Diastolic	16	85	9	14	79	9	30	82	9	0.08
Heart rate, bpm	16	73	13	14	75	15	30	74	14	0.76
Liver function variables										
AST, U/L	16	30.2	13.0	14	34.4	17.1	30	32.1	14.9	0.46
ALT, U/L	16	40.0	20.9	14	47.2	28.7	30	43.4	24.7	0.43
AST:ALT ratio	16	0.91	0.59	14	0.81	0.25	30	0.87	0.46	0.56
GGT, U/L	16	45.4	34.9	14	45.0	34.3	30	45.2	34.0	0.98
Lipids										
LDL cholesterol, mmol/l	16	2.2	0.9	14	2.4	1.0	30	2.3	0.9	0.29
HDL cholesterol, mmol/l	16	1.2	0.3	14	1.2	0.3	30	1.2	0.3	0.62
Triglycerides, mmol/l	16	1.5	0.6	14	1.8	0.9	30	1.6	0.8	0.88
NAFLD/fibrosis scores										
FLI	16	78.3	19.4	14	77.9	17.4	30	78.1	18.2	0.96
FIB-4	16	1.46	0.81	14	1.40	0.64	30	1.42	0.72	0.81
		n/N	%		n/N	%		n/N	%	
Female sex		6/16	37.5		4/14	28.6		10/30	33.3	0.71
White ethnicity		15/16	93.8		14/14	100		29/30	96.7	0.0
Alcohol		10/16	62.5		9/14	64.3		19/30	63.3	0.92
Smoking		4/16	25.0		1/14	7.1		5/30	16.7	0.19
Steatosis hepatitis		11/16	68.8		11/14	78.6		22/30	73.3	0.54

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; DAPA, dapagliflozin; EXE, exenatide; FIB-4, fibrosis 4 score; FLI, fatty liver index; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated haemoglobin; HCL, hepatocellular lipid; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; n, number; NAFLD, nonalcoholic fatty liver disease; PLAC, placebo; SAT, subcutaneous adipose tissue; SD, standard deviation; VAT, visceral adipose tissue. * Variables were log-transformed.

TABLE 2 Comparison of the EXE + DAPA and the PLAC + DAPA groups after 24 weeks of treatment, adjusted for the baseline outcome variables and for sex, age, BMI at baseline and the baseline outcome variable

	N	Adjustment for baseline outcome variable Mean difference	95% CI	P	Multiple adjustment Mean difference	95% CI	P
Lipid distribution							
HCLs, %	30	-0.65	-4.40 to 3.10	0.72	-0.77	-4.84 to 3.30	0.70
VAT, mm ²	26	-0.10	-1.02 to 0.82	0.82	0.06	-1.01 to 1.13	0.91
SAT, mm ²	26	-0.66	-2.53 to 1.21	0.47	-0.43	-2.41 to 1.55	0.66
Glycaemic variables							
HbA1c, mmol/mol	30	-6.0	-9.7 to -2.2	<0.01	-0.52	-0.86 to -0.17	<0.01
Fasting glucose, mmol/mol	30	-0.7	-1.4 to -0.07	0.03	-0.6	-1.3 to 0.0	0.051
Fasting insulin, µU/mL	30	4.23	-4.19 to 12.65	0.31	3.69	-5.28 to 12.65	0.40
HOMA-IR	30	0.89	-1.41 to 3.18	0.44	0.44	-2.10 to 2.98	0.73
Anthropometrics							
Weight, kg	30	-2.32	-5.84 to 1.21	0.19	-2.45	-5.45 to 0.54	0.10
BMI, kg/m ²	30	-0.70	-1.78 to 0.38	0.19	-0.62	-1.70 to 0.47	0.25
Waist circumference, cm	30	-0.07	-2.89 to 2.76	0.96	0.02	-3.00 to 3.04	0.99
Hip circumference, cm	30	0.07	-3.51 to 3.66	0.97	0.36	-3.45 to 4.16	0.85
Liver function variables							
AST, U/L	30	-0.20	-5.18 to 4.79	0.94	0.28	-5.06 to 5.62	0.92
ALT, U/L	30	-1.72	-11.76 to 8.33	0.73	-0.85	-11.65 to 9.94	0.87
AST:ALT ratio	30	0.05	-0.10 to 0.20	0.50	0.05	-0.09 to 0.20	0.48
GGT, U/L	30	2.17	-8.68 to 13.03	0.69	3.18	-8.10 to 14.47	0.57
Lipids							
LDL cholesterol, mmol/l	30	-0.34	-0.83 to 0.15	0.17	-0.31	-0.82 to 0.19	0.21
HDL cholesterol, mmol/l	30	-0.05	-0.15 to 0.06	0.36	-0.04	-0.15 to 0.07	0.45
Triglycerides, mmol/l	30	0.08	-0.20 to 0.36	0.57	0.09	-0.20 to 0.38	0.53
NAFLD/fibrosis scores							
FLI	30	0.87	-8.66 to 10.39	0.85	1.87	-8.06 to 11.81	0.70
FIB-4	30	0.11	-0.09 to 0.32	0.27	0.12	-0.09 to 0.34	0.25

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; DAPA, dapagliflozin; EXE, exenatide; FIB-4, fibrosis 4 score.; FLI, fatty liver index; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated haemoglobin; HCL, hepatocellular lipid; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; n, number; NALFD, nonalcoholic fatty liver disease; PLAC, placebo; SAT, subcutaneous adipose tissue; SD, standard deviation; VAT, visceral adipose tissue.

3.2 | Glycaemic control and efficacy

Fasting glucose and HbA1c significantly decreased in both the EXE + DAPA and the PLAC + DAPA groups and were significantly lower in the EXE + DAPA compared with the PLAC + DAPA group at end of study (Tables 2 and 3, Figure 2). Homeostatic model assessment of insulin resistance (HOMA-IR) was significantly lower in the PLAC + DAPA group, but no differences in HOMA-IR between treatment groups were found. At 24 weeks, HbA1c <48 mmol/mol (6.5%) was observed in 11/16 participants (68.8%) compared with 0/16 at baseline ($P = 0.001$) in EXE + DAPA and 5/14 participants (35.7%) versus 2/14 (14.3%; $P = 0.25$) in the PLAC + DAPA group. Logistic regression analysis adjusted for baseline outcome levels identified significant differences in treatment efficacy (HbA1c <48 mmol/mol) and higher reductions in EXE + DAPA (relative risk 0.15, 95% confidence interval 0.03; 0.81; $P = 0.028$).

3.3 | Weight and anthropometrics

After 24 weeks of treatment BMI, weight, and waist and hip circumference were significantly lower in the EXE + DAPA and PLAC + DAPA groups, with no significant difference found between the two treatment arms (Tables 2 and 3, Figure 2).

3.4 | Liver function parameters

At end of study, AST was significantly lower in both treatment groups, whereas ALT was significantly lower in the EXE + DAPA group and showed only a trend towards lower levels in the PLAC + DAPA group. GGT was significantly reduced in the PLAC + DAPA group only. No between-group differences were found in

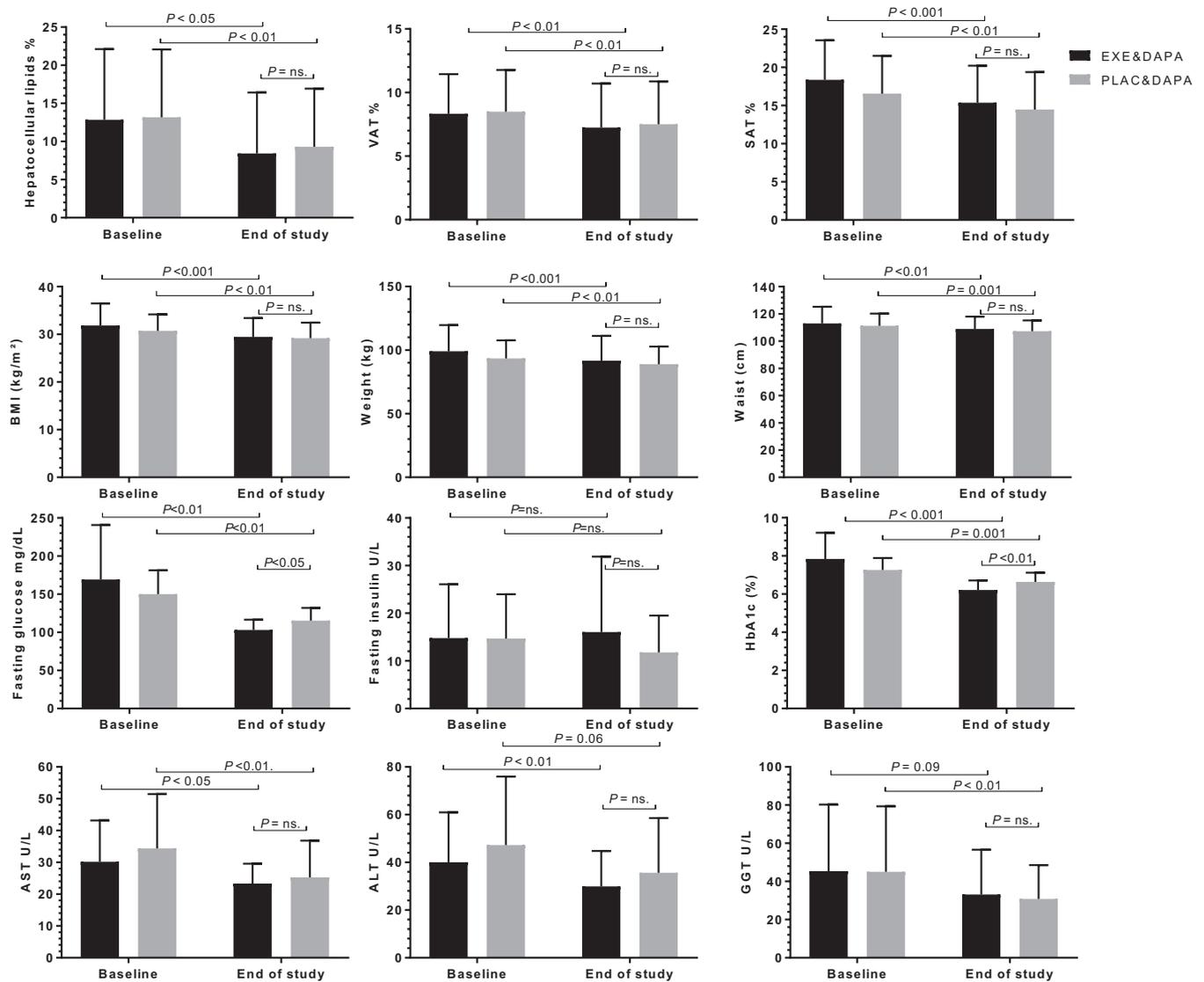


FIGURE 2 Ectopic lipids, visceral and subcutaneous fat, glycaemic, anthropometric and liver function variables at baseline and 24 weeks after treatment with exenatide (EXE) + dapagliflozin (DAPA) and placebo (PLAC) + DAPA. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transpeptidase; ns, not significant; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue

any of the three variables at end of study (Tables 2 and 3, Figure 2).

3.5 | Lipids

After 24 weeks of treatment low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides did not differ between treatment groups. LDL and HDL cholesterol did not change significantly from baseline, whereas triglycerides significantly decreased in the PLAC + DAPA group and were close to significant in the EXE + DAPA group (Tables 2 and 3).

3.6 | Calculated predictors of NAFLD and fibrosis

No differences between groups were found at end of study in fatty liver index (FLI) or fibrosis 4 score (FIB-4; Tables 2 and 3). FLI was significantly lower in both treatment groups. FIB-4 was significantly lower in the PLAC + DAPA group.

3.7 | Correlations

Correlation analysis demonstrated that the primary outcome variable HCL level was associated with changes in weight ($r = 0.54$, $P = 0.002$), hip circumference ($r = 0.40$, $P = 0.03$), waist

TABLE 3 Within-group changes after 24 weeks of treatment in the total group and in the combined EXE + DAPA and PLAC + DAPA groups

	Total changes before - after analysis		P for change from baseline to week 24		Before - after EXE + DAPA		Before - after PLAC + DAPA	
	Mean reduction (BL to EOS)	95% CI	N	P	Mean reduction (BL to EOS)	95% CI	Mean reduction (BL to EOS)	95% CI
Lipid distribution								
HCLs absolute, %	-4.14	-6.30 to -1.99	16	<0.001	-4.41	-8.16 to -0.67	-3.87	-6.04 to -1.69
VAT, mm ²	-1.04	-1.49 to -0.59	14	<0.001	-1.09	-1.77 to -0.41	-0.99	-1.63 to -0.34
SAT, mm ²	-2.54	-3.48 to -1.59	14	<0.001	-3.00	-4.38 to -1.62	-2.08	-3.56 to -0.65
Glycaemic variables								
HbA1c, mmol/l	-12.7	-17.1 to -8.3	16	<0.001	-17.8	-24.8 to -10.8	-6.9	-10.5 to -3.3
Fasting glucose, mmol/l	-2.9	-4.1 to -1.7	16	<0.001	-3.7	-5.7 to -1.7	-1.9	-3.2 to -0.7
Fasting insulin, µU/mL	-2.19	-9.71 to 5.33	16	0.56	1.27	-6.71 to 9.24	-2.97	-6.48 to 0.63
HOMA-IR	-2.13	-3.70 to -0.56	16	<0.01	-2.17	-4.68 to -0.35	-2.10	-4.11 to -0.09
Anthropometrics								
Weight, kg	-5.96	-7.75 to -4.17	16	<0.001	-7.34	-9.87 to -4.82	-4.57	-7.36 to -1.79
BMI, kg/m ²	-1.97	-2.57 to -1.38	16	<0.001	-2.43	-3.26 to -1.60	-1.52	-2.45 to -0.59
Waist circumference, cm	-3.56	-5.56 to -2.36	16	<0.001	-4.23	-6.82 to -1.63	-3.69	-5.67 to -1.71
Hip circumference, cm	-4.91	-6.77 to -3.05	16	<0.001	-5.00	-7.59 to -2.41	-4.81	-7.74 to -1.89
Liver function variables								
AST, U/L	-7.97	-12.01 to -3.92	16	<0.001	-6.88	-13.39 to -0.36	-9.07	-14.17 to -3.97
ALT, U/L	-10.85	-17.20 to -4.49	16	0.002	-10.13	-16.94 to -3.31	-11.57	-23.55 to 0.41
AST:ALT ratio	0.11	-0.20 to 0.42	16	0.46	0.02	-0.15 to 0.10	0.01	-0.13 to 0.13
GGT, U/L	-13.23	-22.17 to -4.30	16	0.005	-12.25	-26.50 to 1.99	-14.21	-25.74 to -2.69
Lipids								
LDL cholesterol, mmol/l	-0.20	-0.51 to 0.11	16	0.20	-0.31	-0.81 to 0.19	-0.07	-0.47 to 0.33
HDL cholesterol, mmol/l	0.06	0.01 to 0.11	16	0.03	0.04	-0.03 to 0.10	3.36	-0.01 to 0.19
Triglycerides, mmol/l	-0.36	-0.55 to -0.17	16	0.001	-0.26	-0.53 to 0.02	-0.48	-0.77 to -0.19
NAFLD/fibrosis scores								
FLI	-12.81	-17.54 to -8.07	16	<0.001	-12.37	-19.23 to -5.52	-13.30	-20.77 to -5.83
FIB-4	-0.22	-0.39 to -0.05	16	0.014	-0.18	-0.45 to 0.09	-0.26	-0.49 to -0.03

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; BMI, body mass index; DAPA, dapagliflozin; EOS, end of study; EXE, exenatide; FIB-4, fibrosis 4 score; FLI, fatty liver index; GGT, gamma-glutamyl transpeptidase; HbA1c, glycated haemoglobin; HCL, hepatocellular lipid; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; n, number; NAFLD, nonalcoholic fatty liver disease; PLAC, placebo; SAT, subcutaneous adipose tissue; SD, standard deviation; VAT, visceral adipose tissue.

circumference ($r = 0.40$, $P = 0.03$), VAT ($r = 0.41$, $P = 0.04$) and SAT ($r = 0.62$, $P = 0.001$), but not with changes in glycaemic variables (HOMA-IR, $r = -0.10$, fasting glucose, $r = 0.23$, HbA1c, $r = 0.33$; all nonsignificant).

3.8 | Adverse events

In total, 24/30 participants reported adverse events (AEs) in our study, with a total of 89 different AEs reported (Appendix S1, supplementary material S5). No hypoglycaemic event (glucose <3.9 mmol/l, symptomatic or asymptomatic, lowest self-reported glucose value = 4.3 mmol/l) and no ketoacidosis occurred. Genital mycosis occurred in 4/16 participants in the EXE + DAPA group and 1/14 participants in the PLAC + DAPA group (25.0% vs. 7.1%; $P =$ nonsignificant). Three of these infections were in women. Urinary tract infections occurred in two participants, one in each treatment group. Gastrointestinal side effects were reported in 4/16 participants in the EXE + DAPA group and 1/14 in the PLAC + DAPA group (25.0 vs. 7.7%; $P =$ nonsignificant). Local skin reactions at the injection site were reported in 2/16 participants in the EXE + DAPA group and 1/14 participants in the PLAC + DAPA group (12.5% vs. 7.1%, $P =$ nonsignificant).

Three serious AEs occurred, which resolved immediately after treatment and were not related to study medication (otitis media, hypertensive crisis, vertigo).

4 | DISCUSSION

As one of the first studies assessing the synergistic effects of a combined GLP-1RA and SGLT2 inhibitor therapy on HCLs quantified by MRS, EXENDA revealed a significant reduction in HCL levels after 24 weeks of treatment in both the EXE + DAPA and PLAC + DAPA groups. However, we were not able to identify differences between these treatment groups, arguing against an additive effect of EXE combined with DAPA, despite better glycaemic control in the EXE + DAPA group, at least during 6 months of treatment. Weight reduction and decreases in hip and waist measures, as well as reduction of VAT and SAT, were significant in both groups, but also did not differ between groups. Furthermore, decreases in liver function variables (AST) were observed in both groups, with again no differences found between groups after 24 weeks.

Consistent with our results, several SGLT2 inhibitors and GLP-1RAs have been associated with improvement of NAFLD.^{18–27} Studies investigating the effects of DAPA on NAFLD in patients with T2DM corroborate our findings and found significantly decreased hepatic fat assessed by MRS, markers of liver injury and VAT, decreased steatosis and fibrosis assessed by transient elastography, along with improved glycaemic control after 8 to 24 weeks of treatment.^{22–24} Interestingly, a recently published real-world observational study observed reductions in HCL only in patients receiving an SGLT2 inhibitor and not in patients receiving a GLP-1RA, which partly

corroborates the findings of EXENDA of no additive effects in combined EXE + DAPA and effects on HCL mainly driven by SGLT2 inhibitor treatment.²⁸ However, other trials are not consistent with these findings, as they found significant decreases of HCL, VAT and SAT measured by MRS in patients with T2DM receiving EXE after 6 months of treatment.^{13,29} Furthermore, lower liver function variables, body weight, waist circumference and postprandial glucose were observed.²⁹

In accordance with our findings, in a secondary analysis of the Duration 8 trial, Gastaldelli et al¹² found a significant reduction in FLI—a measure that has high correlation with HCLs—after 28 weeks of treatment in all of their three treatment arms, combined EXE + DAPA, and EXE or DAPA monotherapy.¹² In contrast to our findings, the combined EXE + DAPA group showed strongest effects on markers of hepatic steatosis and fibrosis, with superior improvements observed for biomarkers of fatty liver/steatosis compared with each monotherapy.¹² However, the combined EXE + DAPA group in Duration 8 had significantly greater weight loss compared to the monotherapy groups after 28 weeks of treatment.¹² This was corroborated in a recently published study testing a combination of liraglutide and canagliflozin compared with monotherapies of canagliflozin or liraglutide.⁹ In our EXENDA trial we were not able to detect significant differences in weight loss in EXE + DAPA compared with PLAC + DAPA, which might serve as an explanation for the similar decrease in HCL levels in both treatment arms. The weight reduction in the PLAC + DAPA group (−4.6 kg) was relatively high compared with a systematic review assessing weight loss in patients with T2DM receiving DAPA (−1.6 kg), possibly leading to higher HCL reduction in the PLAC + DAPA group.³⁰ Interestingly, an earlier study reported greater weight reduction in patients with longer diabetes duration (11 years) compared with patients with a short T2DM duration (1 year) after treatment with DAPA for 12 weeks.³¹ The reason for this difference was not clear, but changes in food intake or metabolic rate were discussed.³¹ In the present study we did not find any associations between diabetes duration and weight or HCL reduction (data not shown).

We found significant associations of HCL with changes in weight, anthropometric variables and, especially, visceral and abdominal fat in the total study population. In Duration 8 significant direct associations of weight loss with ALT:AST ratio, as well as indirect treatment effects on ALT:AST ratio and adipose tissue insulin resistance index (Adipo-IR) mediated by weight loss in EXE + DAPA, compared with the other treatment groups were found.¹² A recent systematic review applying different weight loss interventions (behavioural, pharmaceutical and surgical) reported evidence of associations between different weight loss treatment options and improved NAFLD biomarkers.³² Significant associations were found between weight loss interventions and the amelioration of laboratory, radiological and histological markers of NAFLD. Thus weight loss interventions are essential recommendations for the treatment of NAFLD in guidelines.²

Results of the Diabetes Remission Clinical Trial (DiRECT) support the above data in a T2DM population and found significant reductions in HCLs in their participants with T2DM, who had an average

decrease of 15% of body weight with reversible β -cell function found predominately in those patients with shorter T2DM duration.³³ According to these results, the remission of T2DM seems to be associated with a reduction in HCL. Ameliorations of fasting glucose levels and hepatic insulin resistance and hepatocellular insulin signalling were associated with decreases in HCL in previous studies.^{3,34} Our findings of significantly improved glucose variables, along with significant reductions in HCLs, support these observations. However, no direct associations were found. We observed significantly lower HbA1c and fasting glucose levels in the EXE + DAPA versus the PLAC + DAPA group, which is in accordance with the findings of Duration 8, with superior effects on glucometabolic variables in the EXE + DAPA group.⁸ However, opposing results were seen in a study combining liraglutide and canagliflozin with absence of the synergistic effect on glucometabolic variables.⁹ Further research is necessary to investigate the mechanisms of additive effects of GLP-1RAs and SGLT2 inhibitors on glucose metabolism.

A main limitation of this study is that it was a pilot trial with low participant numbers and therefore outcomes should to be considered as exploratory and analysed with care. Further trials will be needed to assess the synergistic effects of GLP-1RAs and SGLT2 inhibitors on HCL. Furthermore, our method for assessing HCLs was MRS, which is not the "gold standard" for NAFLD assessment. Nonetheless, it is a highly reliable and accurate, noninvasive method, with good correlation with histological methods, and can assess lipid distribution in liver and other organs in one session and with relatively short duration.³⁵ However, measurement facilities are limited and MRI costs are high. Another limitation was the fact that HCL was not defined as an inclusion criterion and thus patients with low hepatic lipid content participated in EXENDA.

In conclusion, EXENDA, one of the first studies in this area, demonstrated improvements in HCLs in a combined GLP-1RA and SGLT2 inhibitor intervention group and an SGLT2 inhibitor comparator group, measured with MRS. While earlier studies showed a potential beneficial additive effect on calculated steatosis/fibrosis scores in their combined treatment group, we were not able to confirm these findings, although significantly better glycaemic control was achieved. Weight reduction seems to play an essential role in the disease-modifying effects on NAFLD. Further studies will be required to assess the potential additive effects of GLP-1RAs and SGLT2 inhibitors on ectopic lipid accumulation and other potential comorbidities.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Jürgen Harreiter was the study coordinator and co-principal investigator, initiated and designed the study, performed the statistical analyses, wrote the first draft of the paper, and edited and finalized the manuscript. Alexandra Kautzky-Willer was the co-principal investigator and sponsor of the study and designed and executed the EXENDA study, provided input for the interpretation of the results, and read and corrected draft versions. Jürgen Harreiter and Alexandra Kautzky-Willer applied for and received funding from AstraZeneca. Ivica Just, Radka Klepochova and Martin Krššák acquired and processed MRS data, read and corrected the draft version and approved the final manuscript. Michael Leutner, Magdalena Bastian, Helmut Brath and Christian Schelkshorn contributed to the conception of the trial, read and corrected draft versions of the manuscript and approved the final manuscript. Jürgen Harreiter and Alexandra Kautzky-Willer are the guarantors of the study.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

ORCID

Jürgen Harreiter  <https://orcid.org/0000-0003-2508-9403>

Alexandra Kautzky-Willer  <https://orcid.org/0000-0002-3520-4105>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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